There is nothing in which the birds differ more from man than the way in which they can build yet leave a landscape as it was before.

Robert Straughton Lynd, American sociologist (1892-1970)

Forum

New Mouse Is a Knockout

Scientists have a new tool to help them unravel the mysteries of the toxicity of dioxin. The development of the aryl hydrocarbon receptor-deficient mouse was reported by Frank Gonzalez and colleagues of the National Cancer Institute this May in *Science*.

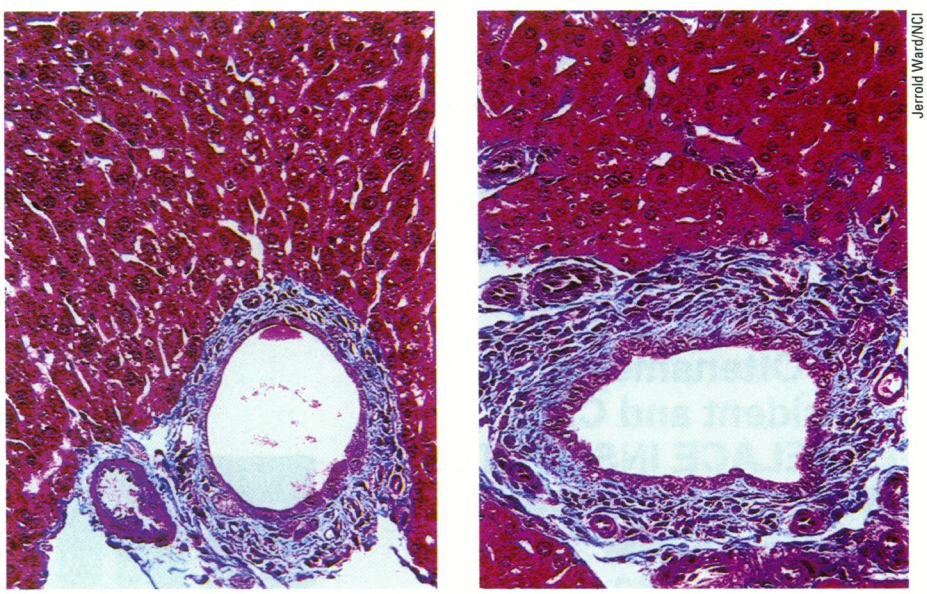
The controversy about the health effects of dioxin partly involves questions about how its toxicity is mediated. Most scientists agree that dioxin exerts its effects by binding to the aryl hydrocarbon receptor (AhR). What is not clear is how this binding relates to the particular cell types that are affected.

The AhR-deficient mouse will help answer questions about the mechanism of dioxin and similar compounds such as benzo[*a*]pyrene, PCBs, and PBBs. Gonzalez and his team produced the mouse by "knocking out" the gene that encodes the AhR. It is known that the AhR detoxifies poisons, but the NCI researchers found evidence that it has other important functions as well.

Half of the AhR-deficient mice die within a week after birth due to a lack of lymphocytes that leaves them susceptible to opportunistic infections. The mice that do survive have massive liver scars and only slowly build up the normal number of lymphocytes. At 10 weeks of age, the animals begin to lose the lymphocytes they built up and eventually become sick due to an incompetent immune system and liver problems. The livers of these mice are 50% smaller than normal, and they have bile duct fibrosis.

The AhR is obviously vital to immune function and liver health. But the depression of the immune system of AhR-deficient mice is a puzzle because the thymus, where T-lymphocytes mature, is normal in these animals. Gonzalez and co-workers hypothesize that AhR-deficient mice may lack a specific lymphoid population or have a systemic defect in the ability of lymphocytes to reside in the peripheral immune system (which includes the reticuloendothelial system, of which the liver is a component). Loss of the AhR may affect thymic processes or affect the migration of cells from the bone marrow (where precursor lymphocytes originate) to the thymus or to peripheral lymphoid organs. Alternatively, the normal life span of peripheral lymphocytes may be shortened in these animals.

Previous research has shown that the AhR may also play a role in brain development. Levels of AhR are high in the fetal neural tube, which gives rise to the central nervous system. Levels decrease after birth. In addition, AhR is found in the kidneys, lungs, and hearts of adults. It is hoped that the AhR-deficient mouse will help clarify the functions of the receptor. However, Gonzalez cautions that experiments with these mice may be difficult because of their poor health. Further genetic engineering may have to be done to turn on the AhR gene only in liver tissue so that the mice will be hardy enough to withstand testing.



Jerrold Ward/NCI

Liver trouble. Accumulation of collagen (blue) around the liver bile duct of a 30-day-old AhR knockout mouse (right) shows the beginning of fibrosis. (Left) Liver bile duct of a normal mouse.

More Muddy Water

In the wake of a report that healthy people can be infected with infinitesimal exposures to *Cryptosporidium* comes the Natural Resources Defense Council's assertion that at least 45 million Americans are at risk of imbibing the diarrhea-causing protozoan in what appears to be clean drinking water.

At the University of Texas in Houston, infectious disease expert Herbert L. DuPont gave 112 healthy volunteers preparations containing between 30 and 1 million *Cryptosporidium* oocysts (the form in which the microbes are found in water). Monitoring enteric symptoms and analyzing stool samples for excreted oocysts, DuPont found that, for the strain he used, the median infective dose was only 132 oocysts. The study suggested the size of the dose did not affect the microbes' incubation period or the severity of the infection.

Just how many people may become infected from their drinking water is impossible to estimate. The NRDC figure of 45 million is based on a survey mailed to 100 of the nation's 61,000 water suppliers, says the organization's president, Eric Olson. The systems who responded serve only a fraction of Americans.

Cryptosporidia give rise to dormant oocysts that remain viable for months in sewage, runoff from feedlots, or groundwater until they find a new host. Unlike other waterborne organisms, the oocysts are neither killed by chlorine nor screened by standard filters, says DuPont. When one member of a household is infected, secondary spread can occur.

Once thought to infect only animals, especially young cattle, *Cryptosporidium* came to the attention of health authorities